Title
Tetramethylenedisulfotetramine

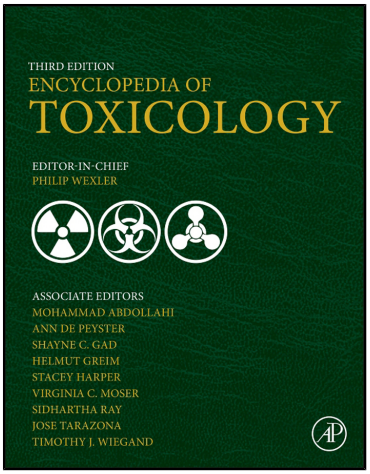
ISBN
9780123864550

Authors
Banks, CN
Yang, D
Lein, PJ
et al.

Publication Date
2014

DOI
10.1016/B978-0-12-386454-3.01055-1

Peer reviewed



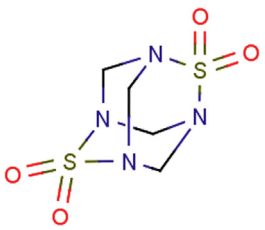
From Banks, C.N., Yang, D.I., Lein, P.J., Rogawski, M.I.I., 2014.
Tetramethylenedisulfotetramine. In: Wexler, P. (Ed.), Encyclopedia of Toxicology, 3rd edition vol 4. Elsevier Inc., Academic Press, pp. 509–511.
ISBN: 9780123864543

Academic Press

Tetramethylenedisulfotetramine

CN Banks, D Yang and PJ Lein, School of Veterinary Medicine, University of California, Davis, CA, USA
MA Rogawski, School of Medicine, University of California, Davis, CA, USA

- Name: Tetramethylenedisulfotetramine
- Chemical Abstracts Service Registry Number: 80-12-6
- Synonyms: 2,6-Dithia-1,3,5,7-tetraazaadamantane,2,2,6,6-Tetraoxide; Tetramine; TETS
- Chemical Formula: C_4–H_8–N_4–O_4–S_2
- Chemical Structure:



Background

Tetramethylenedisulfotetramine (2,6-dithia-1,3,5,7-tetraazadamantane,2,2,6,6-tetraoxide, TETS) is a highly toxic heteroadamantane rodenticide. It is an odorless, tasteless, white crystalline powder that is slightly soluble in water (0.25 mg ml^{-1}), dimethyl sulfoxide and acetone. It was originally synthesized in 1933 as a resinous condensation product of sulfamide and formaldehyde and used commercially in pillows and upholstery as an impregnating stiffening and antimold agent. However, in 1950, a massive poisoning of German workers in the furniture manufacturing industry was linked to 'Crinex' wool, which contained TETS as a byproduct of processing. Early experimental studies in rodents revealed that TETS was an extremely toxic convulsant agent. It was also discovered at this time that TETS is a highly effective rodent repellent, which resulted in its use during reforestation projects to prevent seed predation by rodents. However, because of its high toxicity in mammals, including humans, and its persistence in the environment, many countries banned its production and use in 1984. This ban became worldwide when China issued similar restrictions in 1991. However, due to its relative ease of synthesis and low cost, TETS remains available on the black market, particularly in many rural areas of China and in regions outside of China that have large Asian populations.

Uses

Despite the worldwide ban on its production and use, TETS continues to be used illicitly as a rodenticide in various regions of the world. In China, TETS is known as 'Dushuqiang', 'Meishuming,' or 'Shanbudao.' In 2000, the National Poison Control Center of China revealed that 74% of commercial rodenticides contained illegal chemicals, with TETS found in nearly 50% of these pesticides. From 1977 to 2002, it was estimated that there were thousands of cases of TETS poisoning in China, resulting in hundreds of deaths. A more recent analysis indicates that between 1991 and 2010, there were over 14 000 cases of TETS intoxication in China, of which 932 resulted in death. In 2003, the first case of TETS intoxication in the United States was reported: a healthy 15-month-old girl was poisoned following accidental ingestion of a rodenticide imported from China that contained TETS. While many cases are thought to be due to accidental poisonings, there have been numerous reports of TETS being used to intentionally poison humans.

Environmental Fate and Behavior

Although TETS has a relatively low solubility in water (0.25 mg kg^{-1}), it is quite stable, thus making it relatively persistent in the environment. It is reported that TETS retains biological activity in water for 6 weeks to 5 months after preparation. It is believed that TETS bioaccumulates (despite a predicted octanol:water coefficient of 0.07) and that contact with poisoned animals can result in intoxication, as demonstrated by reports of dogs dying after eating TETS-poisoned rats and by Chinese newspapers warning against consuming meat from dogs that were suspected to have eaten TETS-poisoned rats.

Exposure and Exposure Monitoring

The most common route of exposure to TETS is ingestion of contaminated foods with subsequent absorption from oral cavities and the gastrointestinal tract. TETS is also rapidly absorbed from the mucous membranes of the upper respiratory tract, and occupational exposures *via* inhalation have been reported. TETS is not absorbed dermally through intact skin, although skin abrasions at the area of exposure greatly enhance dermal absorption. Currently, the only effective means for monitoring TETS exposure is by gas chromatography coupled to mass spectrometry (GC/MS) of urine, blood, or vomitus samples. Advances in GC/MS methodologies to detect TETS permit the detection of impurities that allow for discrimination of synthesis routes and batch to batch variation, which may better help forensic investigators determine individual sources of TETS in cases of poisoning.

Toxicokinetics

TETS distributes to most major organs of the body. The half-life of TETS was originally estimated to be approximately 2–3 days based on studies using intraperitoneal administration in rats. Later studies in rabbits demonstrating that the plasma half-life of TETS is 56.9 h following intravenous injection and 262.5 h

Encyclopedia of Toxicology, Third Edition, 2014, 509–511

following oral ingestion suggest that clearance depends on the route of exposure. TETS is excreted unchanged in urine and feces suggesting minimal metabolism.

Mechanism of Toxicity

TETS is a potent convulsant neurotoxicant. TETS has no major effects on peripheral neuromuscular or autonomic transmission and its toxicity appears to be due primarily to actions on the central nervous system. Postmortem studies of TETS-poisoned patients revealed significant pathology in the brain, including degeneration in the basal ganglia, subarachnoid hemorrhages, cerebral and cerebellar bleeding, and brainstem hemorrhages. In cases of extreme intoxication, edema, congestion, and hemorrhages are commonly found in not only the brain but also the heart, lungs, liver, and kidneys. Markers of severe tissue damage (aspartate aminotransferase, alanine aminotransferase, creatine phosphokinase, lactate dehydrogenase, α-hydroxybutyrate dehydrogenase, and creatine phosphokinase isoenzyme MB) are also higher in patients who succumbed to TETS poisoning compared to patients who survived. Additional consequences of TETS intoxication include low potassium levels (hypokalemia), low phosphorus levels (hypophosphatemia), abnormal sodium levels (hypo- or hypernatremia), metabolic acidosis, circulatory hypoxia, and renal tubular damage as demonstrated by elevated levels of *N*-acetyl-β-D-glucosaminidase and retinol-binding protein. Collectively, these findings are consistent with reports that death following acute TETS intoxication is primarily due to multiple organ dysfunction syndrome.

It is generally believed that the convulsant action of TETS is mediated by noncompetitive reversible antagonism of the $GABA_A$ receptor chloride channel. TETS blocks γ-aminobutyric acid (GABA)-dependent chloride influx in diverse experimental preparations and inhibits the binding of [^{35}S]TBPS to $GABA_A$ receptors. $GABA_A$ receptors are composed of different subunits (α1–α6, β1–β4, γ1–γ3, δ, ε, π, and ρ1–ρ3), and require at least one α, β, and γ subunit to be fully functional. TETS is active on native $GABA_A$ receptors and recombinant α1β3γ2 receptors, but has no effect on recombinant receptors composed entirely of β3 subunits. Picrotoxin, which similarly induces convulsions *via* GABA receptor antagonism, is much more selective for the β3 receptor compared to native receptors and the recombinant α1β3γ2 hetero-oligomer.

While the experimental evidence clearly implicates $GABA_A$ receptor antagonism as a central mechanism underlying the convulsant action of TETS, a number of observations suggest that inhibition of GABA receptor-mediated chloride influx may not be the only mechanism contributing to TETS neurotoxicity. First, *in vivo* recordings in rats demonstrated that intravenous TETS inhibits responses to iontophoretically applied GABA and produces prolonged epileptiform spiking in the cortical electroencephalogram (EEG); however, there is a dissociation between these two effects. Second, despite the fact that TETS and picrotoxin are equipotent in displacing [^{35}S]TBPS from $GABA_A$ receptors and inhibiting chloride channels, TETS is significantly more toxic (lethal dose 50% (LD_{50}) of 0.1 mg kg^{-1} for TETS *versus* 15 mg kg^{-1} for picrotoxin). Third, unlike other toxicants that act at $GABA_A$ receptors (such as pentylenetetrazol), administration of TETS does not induce kindling.

Additional mechanism(s) that contribute to the convulsant activity of TETS have yet to be identified. There are, however, reports of additional biochemical effects that may contribute to the toxic profile of TETS. $GABA_A$ receptors are downregulated in rats following TETS exposure, and GABA levels initially decrease, but rebound above control levels and remain elevated for many days post-exposure. Bcl-2 and caspase-3 expression are elevated in mild to severe cases of intoxication. Caspase-3 cleaves Bcl-2, which promotes the release of cytochrome *C* from the mitochondria, a hallmark of apoptosis. Cytochrome *C* expression is also increased following TETS exposure, providing further evidence that apoptotic processes may be involved in TETS neurotoxicity.

Acute and Short-Term Toxicity

The LD_{50} for TETS is 0.1–0.2 mg kg^{-1}, i.p. in rodents and rabbits, and 7–10 mg is considered to be a lethal dose for an adult human. Mild to moderate intoxication produces numerous symptoms, including headaches, dizziness, nausea, fatigue, vomiting, anorexia, pain, numbness, and lethargy. Severe intoxication produces generalized clonic–tonic convulsions that can progress to status epilepticus, arrhythmias, coma, and death. The time to onset of seizures following exposure to TETS can range from 30 min to 13 h. EEGs in TETS-intoxicated humans reveal mild to moderate abnormalities with increased amplitudes, slower frequencies, and generalized spikes, sharp wave, spike-and-wave, and sharp-and-slow wave complexes. Lethality is generally caused by respiratory arrest and/or multiple organ failure.

Chronic Toxicity

Delayed or long-term effects following acute intoxication have been reported, including abnormal EEG, epileptogenic foci, absence seizures and memory impairments, that persist for months following exposure, and can last more than a year. Additionally, acute TETS poisoning may cause developmental delays in young children, and adversely affect cognitive development, as evidenced by lower verbal, performance, and overall intelligence scores in children exposed to TETS compared to controls. There is no evidence in the human population of toxic effects in response to chronic low-level exposures to TETS and in experimental rodent models, prolonged exposure to sublethal doses of TETS has not been observed to cause any significant histopathology.

Immunotoxicity

TETS elevates serum levels of several inflammatory mediators, including β-endorphins, endothelins, nitric oxide, and tumor necrosis factor α (TNFα). The concentration of these inflammatory molecules is positively correlated with the severity of intoxication and the clinical condition of the patient, as levels were extremely high in patients that did not survive TETS poisoning. However, lipopolysaccharide fails to stimulate cytokine release from monocytes following TETS intoxication, suggesting an impaired immune response. Hemoperfusion restored

cytokine production in surviving patients, but failed to stimulate cytokine release from monocytes in patients that did not survive. Recent experimental evidence shows that acute TETS intoxication induces transient inflammatory responses in the brain, as demonstrated by enhanced activation of astrocytes and microglia in the cortex and hippocampus of TETS-intoxicated mice.

Genotoxicity

TETS causes DNA damage in lymphocytes, brain cells, and cardiac muscle cells of rat, which may trigger apoptosis.

Clinical Management

TETS poisoning is difficult to diagnose, particularly if healthcare providers are unfamiliar with the compound, as is typically the case outside of mainland China. TETS intoxication may be mistaken for poisoning by different substances that elicit similar symptoms, such as organophosphorus anti-cholinesterases. There is no antidote for acute TETS intoxication, and treatment is mainly supportive. Treatments to decrease body burdens of TETS, including gastric lavage, diuresis, catharsis, hemodialysis, and administration of sodium 2,3-dimercapto-1-propanesulfonate (DMPS) are often employed. Of these, DMPS has shown some limited use in treating TETS intoxication in animal studies when administered shortly after exposure, and co-administration of pyridoxine (vitamin B6) with DMPS has been reported to further increase survival when administered at longer periods after TETS exposure. However, there have been no clinical studies to support the efficacy of these approaches in humans. Anti-epileptic medications, including benzodiazepines, are often administered in an attempt to control TETS-induced seizures. However, benzodiazepines, and other anti-convulsant drugs, such as phenytoin and valproate, may have limited efficacy unless administered early after the onset of seizures as the available literature suggests that even aggressive use of these drugs is of limited success, particularly in patients presenting with status epilepticus.

Exposure Standards and Guidelines

There are no exposure standards or guidelines for TETS since it has been banned worldwide since 1991, and all uses of the chemical are illegal.

Further Reading

While more than 2000 clinical reports of TETS intoxication, many of which concerned fatalities, have been published in the Chinese scientific literature. There are relatively few reports of TETS toxicity available in peer-review scientific journals published in English. Listed below is a subset of the latter.

Barrueto, F., Furdyna, P.M., Hoffman, R.S., Hoffman, R.J., Nelson, L.S., 2003. Status epilepticus from an illegal imported Chinese rodenticide: "tetramine". J. Toxicol. Clin. Toxicol. 41 (7), 991–994.

Croddy, E., 2004. Rat poison and food security in the People's Republic of China: focus on tetramethylene disulfotetramine (tetramine). Arch. Toxicol. 78, 1–6.

Whitlow, K.S., Belson, M., Barrueto, F., Nelson, L., Henderson, A.K., 2005. Tetramethylenedisulfotetramine: old agent and new terror. Ann. Emerg. Med. 45 (6), 609–613.

Zhang, Y., Su, M., Tian, D.P., 2011. Tetramine poisoning: a case report and review of the literature. Forensic Sci. Int. 204, e24–e27.